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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/511,383	05/18/2005	Alexander L. Klibanov	022078-000002	5031

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WOODARD, EMHARDT, MORIARTY, MCNETT & HENRY LLP
111 MONUMENT CIRCLE, SUITE 3700
INDIANAPOLIS, IN 46204-5137

EXAMINER	
DIBRINO, MARIANNE NMN	

ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
12/29/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

DocketDept@uspatent.com

Office Action Summary	Application No.	Applicant(s)	
	10/511,383	KLIBANOV ET AL.	
	Examiner	Art Unit	
	MARIANNE DIBRINO	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 August 2009 and 22 December 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-35* is/are pending in the application.

4a) Of the above claim(s) *21-29,31,34 and 35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20,30,32 and 33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/5/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment filed 8/24/09 and Applicant's response filed 12/22/08 are acknowledged and have been entered.

2. Applicant is reminded of Applicant's election with traverse of Group I and species of membrane comprising a lipid, fluorine-containing gas, mean diameter of about 1 to 10 micrometers, membrane comprising an antibody and diagnostic composition useful for ultrasound imaging in Applicant's responses filed 7/15/08 and 11/5/07, respectively.

Claims 1-20, 30, 32 and 33 are presently being examined.

3. Applicant's amendment filed 8/24/09 has overcome the prior rejection of record of claims 1-15, 30, 32 and 33 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

4. For the purpose of prior art rejections, the filing date of the instant claims is deemed to be the filing date of PCT/US03/21712, *i.e.,* 7/11/03, as the provisional parent application 60/395,179 does not support the claimed limitations of the instant application.

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

6. Claims 1-20, 30, 32 and 33 are rejected under 35 U.S.C. 102(b) as being anticipated by U.S. 6,193,951 B1.

Claims 16-20 were previously rejected upon the basis set forth below in the prior Office Action of record. The inclusion of claims 1-15, 30, 32 and 33 is necessitated by Applicant's amendment filed 8/24/09.

U.S. 6,193,951 B1 discloses microparticules or microbubbles in a liquid medium, said microparticles or microbubbles comprising a membrane and containing a gas including a fluorocarbon gas *i.e.,* a fluorine-containing gas), liquid or solid for use as a contrast agent for ultrasonic contrast imaging. U.S. 6,193,951 B1 discloses that the microbubbles may be non-spherical, and about 1 micron to less than about ten microns in order to pass through the capillaries of the circulatory system. U.S. 6,193,951 B1 discloses that the membranes may be made from proteins or polymers and may be altered to include a targeting moiety such as antibodies or fragments thereof for binding to selected tissues such as to cell surface receptors. U.S. 6,193,951 B1 discloses use of a blood insoluble gas within the microbubbles (see entire reference).

It is an inherent property that non-spherical microbubble membranes exhibit increased deformability under shear relative to corresponding spherical microbubble membranes.

With regard to the limitation "wherein at least 20%" or "greater than 50%" of the gas-filled microbubbles are nonspherical, the art reference discloses methods intended to convert the majority of the microbubbles to nonspherical microbubbles.

With regard to the limitation "nonspherical microbubbles having microbubble membranes with exterior surfaces comprising outwardly-projecting wrinkles formed of excess membrane material", although the art reference does not explicitly teach this limitation, the art reference does teach that the volume of the microbubble decreases as it is made to shrink and that it is nonspherical. Therefore, the claimed composition appears to be the same as the compositionof the prior art absent a showing of differences. Since the Patent Office does not have the facilities for examining and comparing the composition of the instant invention to those of the prior art, the burden is on applicant to show a distinction between the composition of the instant invention and that of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

Applicant's arguments have been fully considered but are not persuasive.

Applicant's said arguments are of record on page 18 of the response filed 12/22/08, that the reference does not disclose the claimed feature of having non-spherical microbubble membranes having exterior surfaces comprising outwardly-projecting wrinkles formed of excess membrane material.

However, while the art reference does not explicitly teach the said limitation, it inherently teaches it.

7. Claims 1-20, 30, 32 and 33 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. 6,193,951 B1.

Claims 16-20 were previously rejected upon the basis set forth below in the prior Office Action of record. The inclusion of claims 1-15, 30, 32 and 33 is necessitated by Applicant's amendment filed 8/24/09.

U.S. 6,193,951 B1 discloses microparticules or microbubbles in a liquid medium, said microparticles or microbubbles comprising a membrane and containing a gas including a fluorocarbon gas *i.e.*, a fluorine-containing gas), liquid or solid for use as a contrast agent for ultrasonic contrast imaging. U.S. 6,193,951 B1 discloses that the microbubbles may be non-spherical, and about 1 micron to less than about ten microns in order to pass through the capillaries of the circulatory system. U.S. 6,193,951 B1 discloses that the membranes may be made from proteins or polymers and may be altered to include a targeting moiety such as antibodies or fragments thereof for binding to selected tissues such as to cell surface receptors. U.S. 6,193,951 B1 discloses use of a blood insoluble gas within the microbubbles (see entire reference).

It is an inherent property that non-spherical microbubble membranes exhibit increased deformability under shear relative to corresponding spherical microbubble membranes.

With regard to the limitation "wherein at least 20%" or "greater than 50%" of the gas-filled microbubbles are nonspherical, the art reference discloses methods intended to convert the majority of the microbubbles to nonspherical microbubbles.

With regard to the limitation "nonspherical microbubbles having microbubble membranes with exterior surfaces comprising outwardly-projecting wrinkles formed of excess membrane material", although the art reference does not explicitly teach this limitation, the art reference does teach that the volume of the microbubble decreases as it is made to shrink and that it is nonspherical. Therefore, the claimed composition appears to be the same as the compositionof the prior art absent a showing of differences. Since the Patent Office does not have the facilities for examining and comparing the composition of the instant invention to those of the prior art, the burden is on applicant to show a distinction between the composition of the instant invention and that of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

Applicant's arguments have been fully considered but are not persuasive.

Applicant's said arguments are of record on page 18 of the response filed 12/22/08, that the reference does not disclose the claimed feature of having non-spherical microbubble membranes having exterior surfaces comprising outwardly-projecting wrinkles formed of excess membrane material.

However, while the art reference does not explicitly teach the said limitation, it inherently teaches it.

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 1-20, 30, 32 and 33 stand rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. 6,372,195 B1 (IDS reference) in view of U.S. 6,548,048 B1 (IDS reference) as evidenced by an admission in the instant specification on page 16 at lines 14-27 and page 17 at lines 1-8.

U.S. 6,372,195 B1 discloses microbubbles that are made in a container by loading two gases, one of which is leached out after the microbubbles are formed, reducing the volume of the microbubbles each by about 75%. U.S. 6,372,195 B1 further discloses that the microbubble membranes are made of one or more surfactants such as carbohydrates, fatty acid esters of sugars, proteins or proteinaceous materials, or polysaccharides. U.S. 6,372,195 B1 discloses that the gas that is loaded and remains after volume reduction (*i.e.*, the gas osmotic agent) may be fluorine-containing gas, and the size of the microbubbles is not more than about 5 to 10 *um* (*i.e.*, micrometers). U.S. 6,372,195 B1 also discloses that the gas osmotic agent preferably has limited solubility in blood. U.S. 6,372,195 B1 discloses use of compositions comprising microbubbles as ultrasound contrast agents suspended in a pharmaceutically acceptable liquid carrier (see entire reference, especially abstract, column 2 at lines 58-63, column 3 at lines 13-31 and lines 52-67, column 4 at lines 1-15 and lines 32-44, column 5 at lines 33-50, column 6 at lines 24-33, column 35-56, column 13 at lines 63-67, column 14 at lines 1-4 and lines 14-27, Table 1, and claims).

U.S. 6,372,195 B1 does not disclose wherein the microbubble membranes include binding targeting molecules that bind to the target, including wherein the molecules are antibodies.

U.S. 6,548,048 B1 discloses gas-filled, including fluorine-gas containing, microbubble compositions, which membranes are lipopeptides) for use as ultrasound contrast agents, said microbubbles having targeting molecules that are antibodies that have affinity for a particular target site or cells, said microbubbles being no larger than about 10 microns. U.S. 6,548,048 B1 discloses that some of the other targeting vectors may be peptides or proteins that bind to receptors, oligonucleotides, or small molecules (entire reference, especially abstract, column 5 at lines 25-67, column 6 at lines 1-67, column 7 at lines 1-37, claims).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have included a targeting antibody such as disclosed for the targeted microbubble of U.S. 6,548,048 B1 in the microbubble disclosed by U.S. 6,372,195 B1.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to make a targeted ultrasound contrast agent composition.

The admission in the instant specification on page 16 at lines 14-31 and page 17 at lines 1-8 is that a spherical microbubble can be modified by reducing the volume of entrapped gas, wherein the excess membrane material will typically form protrusions from the microbubble membrane, which can be described as crenations, folds, wrinkles or other irregualities, and that at least about 10% of the gas is removed to convert spherical microbubbles to non-spherical microbubbles, but the amount may be higher.

With regard to the limitation "nonspherical microbubbles having microbubble membranes with exterior surfaces comprising outwardly-projecting wrinkles formed of excess membrane material", although the art reference does not explicitly teach this limitation, the art reference does teach that the volume of the microbubble decreases as it is made to shrink, for example, the art reference discloses a 25% reduction in volume after loss of the first gas comprised in said microbubble.

With regard to the limitation "wherein the gas is substantially insoluble in blood" recited in instant claims 3, 12 and 18, the primary art reference discloses that the gas should have limited solubility in blood, and it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used a gas that is substantially insoluble in blood so that the gas would be maintained within the microbubble when it is administered *in vivo*, maintaining ultrasound contrast enhancement.

With regard to the limitation "wherein at least 20%" or "greater than 50%" of the gas-filled microbubbles are nonspherical, the art reference discloses methods intended to convert the majority of the microbubbles to nonspherical microbubbles.

It is an expected property that non-spherical microbubble membranes exhibit increased deformability under shear relative to corresponding spherical microbubble membranes because they are non-spherical and less pressurized than their spherical counterparts.

Therefore the claimed microbubble composition appears to be the similar to the microbubble composition of the prior art absent a showing of unobvious differences. Since the Patent Office does not have the facilities for examining and comparing the composition of the instant invention to those of the prior art, the burden is on Applicant to show an unobvious distinction between the microbubble composition of the instant

invention and that of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

Applicant's arguments have been fully considered but are not persuasive.

Applicant's said arguments are of record on pages18-22 of the response filed 12/22/08, that the reference does not disclose the claimed features that at least 20% of the microbubles in the liquid carrier are nonspherical microbubbles having non-spherical microbubble membranes having exterior surfaces comprising outwardly-projecting wrinkles formed of excess membrane material, nor that the nonspherical microbubbles exhibit increased deformability under shear relative to corresponding spherical microbubbles, nor that the membranes include targeting molecules that bind to the target.

However, while combined references do not explicitly teach the first two said limitations, they implicitly teach them, regardless that the instant specification discloses experimental and result descriptions for attachment events and pause times.

Applicant further argues that one of ordinary skill in the art at the time of invention would more likely have expected upon loss of gas volume that the microbubbles would rapidly transition and shed excess membrane material to again take on a spherical shape, and thus would never have been equipped with information necessary to realize that the claimed wrinkled microbubbles should be prepared and should incorporate a targeting molecule to improve adherence to the target. Applicant provides three references, Borden *et al*, Pu *et al* and Gopal *et al* to support their argument.

However, the primary art reference teaches non-spherical microbubbles and methods to make them. In addition, the Borden *et al* and Pu *et al* references teach air-filled microbubbles of lipid monolayers, whereas the microbubbles of the art references may be filled with fluorine-gas containing compositions, a distinction that might conceivably contribute to the morphology of the resulting microbubble composition (the primary art reference discloses using mixtures of air and fluorine-containing gas and varying the mixture according to the size desired). Pu *et al* also teach that the surface composition and microstructure of the microbubbles also influences deformation and shedding. Gopal *et al* teach morphology and collapse transitions in binary phospholipid monolayers, and also teach that the resulting morphology and transitions are temperature dependent. In contrast the microbubble composition of the instant claims is not confined to binary sphospholipid monolayers that act in a temperature dependent fashion. The evidence presented by Applicant is not commensurate in scope to the instant claims.

10. No claim is allowed.

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

12. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ram Shukla, can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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